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ORIGINAL ARTICLE

Histopathology of excised midurethral sling mesh

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Abstract
Introduction and hypothesis The objective of this study was to compare the histological characteristics of pathological specimens of excised midurethral sling mesh and surrounding vaginal tissue in patients who presented preoperatively with pain and/or exposure of mesh to patients who underwent mesh excision for voiding dysfunction without pain and/or erosion.
Methods This is a retrospective case–control study of women who underwent excision of midurethral sling mesh between 2008 and 2013. Three groups were identified: (1) voiding dysfunction without pain or exposure (control group), (2) pain and/or mesh exposure, and (3) voiding dysfunction with pain and/or mesh exposure. All original pathological specimens were rereviewed by one pathologist blinded to indication for excision and the previous pathology report. Degree of inflammation and fibrosis were recorded based on a 4-point scale along with the presence of giant cell reaction.
Results A total of 130 subjects met inclusion criteria: 60 (46.2 %) with voiding dysfunction only, 21 (16.2 %) with pain/erosion, and 49 (37.7 %) with both pain/exposure and voiding dysfunction. The voiding dysfunction only group was found to have significantly higher levels of inflammation, median grade 2 (1–3), compared to the other two groups with a p value of 0.007. There were no statistical differences in fibrosis and giant cell reaction between the three groups.
Conclusions Midurethral sling mesh excised for voiding dysfunction demonstrates elevated levels of inflammation compared to mesh that is excised for pain and/or exposure. The vaginal tissue fibrosis and giant cell reaction are similar in patients who undergo mesh excision for voiding dysfunction and pain, and/or mesh exposure.

Keywords Foreign body reaction · Mesh erosion · Mesh exposure · Midurethral sling · Vaginal mesh

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Introduction

Known complications of a midurethral sling placement include bladder, bowel, and vascular injury as well as postoperative voiding dysfunction and mesh erosion or exposure [1]. Review of the literature shows that the risk of mesh exposure/erosion after midurethral sling placement ranges from 0.3 to 5.9 % [2–4]. Risk factors associated with mesh exposure/erosion include younger age at time of placement [5], concomitant prolapse surgery [5], and certain synthetic mesh materials [6, 7].

Following the 2008 and 2011 US Food and Drug Administration (FDA) Safety Communication reports on transvaginal mesh use, reported complications of mesh erosion/exposure have increased significantly [8]. As a result, there has been a growing focus on the biomechanics and physical properties of different types of vaginal mesh [9], and efforts to identify patient-centered risk factors for mesh erosion have also increased. Despite these efforts, limited research has been performed on the human host response to synthetic midurethral slings. This is surprising, as research exists on other types of synthetic materials used in surgery. For example, in 1954, Marlex mesh was introduced for abdominal hernia repairs [10], and due to postoperative complications associated with its use numerous research studies were conducted to compare different types of mesh materials and

surgical techniques. This also marked the beginning of laboratory research that focused on the host response to the foreign body. Since then, multiple human and animal studies have identified the host-tissue response as it relates to the placement of different types of mesh in different anatomic locations [11, 12] including many publications on the human tissue response to both synthetic and biological mesh used in the setting of abdominal hernia repair [13, 14].

Vaginal mesh may be excised after midurethral sling placement for different indications, most frequently for mesh exposure and obstructive voiding dysfunction with little known about the underlying histological explanation for these indications. Therefore, the aim of this study was to compare the histological characteristics of pathological specimens of excised midurethral sling mesh and surrounding vaginal tissue in patients who presented preoperatively with pain and/or exposure of mesh to patients who underwent mesh excision for voiding dysfunction without pain or erosion. We hypothesized that the histopathological findings would be different between these two groups, with more inflammation in those with pain and/or mesh exposure.

Materials and methods

This was a retrospective chart review of women who underwent excision of midurethral sling mesh at a tertiary care center from 1 January 2008 through 1 January 2013. Institutional Review Board approval was obtained for this study. Patients were identified by their Current Procedural Terminology (CPT) code (57287) for removal or revision of sling for stress urinary incontinence. Subjects with incomplete documentation or absent pathological specimens were excluded. Once subjects were identified, the healthcare systemwide electronic medical record was queried for patient demographics and pre- and intraoperative data. Operative reports of the index surgery were reviewed if available. Data specific to the index surgery included type of mesh placed, date of surgery, and concomitant procedures. Previous treatment (physical therapy, vaginal estrogen, office-based excision, urethral dilation, and/or pharmacological intervention with anticholinergics) prior to operative mesh excision was also recorded.

Three separate groups were identified based on the indication for midurethral mesh excision: (1) voiding dysfunction without pain or exposure (control group), (2) pain and/or mesh exposure, and (3) voiding dysfunction with pain and/or mesh exposure. The original pathological specimens were rereviewed by a single pathologist blinded to the indication for excision as well as the previous pathology report. Degree of inflammation and fibrosis were recorded on a 4-point scale (range 0–3) developed specifically to compare histological differences at our institution (Table 1). The presence or absence of giant cell reaction was also recorded.

Table 1 Histological grading system

Chronic inflammation	
None (0)	Absent inflammation
Mild (1)	Sparse chronic inflammatory infiltrate, confined to areas of giant cell reaction if present
Moderate (2)	Moderate chronic inflammatory infiltrate in areas of giant cell reaction and involving adjacent connective tissue
Marked (3)	Marked inflammatory infiltrate in areas of giant cell reaction and prominently involving connective tissue; any germinal center formation
Fibrosis	
None (0)	Absent fibrosis
Mild (1)	Predominantly loose connective tissue with focal fibrosis
Moderate (2)	Focal dense fibrosis
Marked (3)	Dense fibrosis with formation of fibrous nodule/plaque

Descriptive statistics were reported as *n*/*N* (%) with 95 % confidence intervals for categorical variables and as mean ±SD and median (range) for all continuous variables. Categorical variables were compared using the chi-square statistic and associations between outcomes were measured using a Fisher's exact test and Pearson's correlation coefficient. Comparisons of outcomes were performed using analysis of variance (ANOVA) for parametric continuous outcomes and Kruskal-Wallis for nonparametric continuous outcomes. For statistically significant results, pairwise comparisons were evaluated with Tukey analysis to identify the differences between the groups. All tests were considered significant at a 0.05 level. JMP 10.0 (SAS, Cary, NC, USA) was used for all statistical analyses.

Results

A total of 191 subjects were identified by our CPT search criteria and 130 subjects of these met inclusion criteria. Mean age was 53.1 years (SD 11.3), average body mass index (BMI) was 29.7 (SD 6.9), and 28.5 % of subjects were identified as current tobacco users at the time of mesh excision. Demographic data did not differ among the three groups (Table 2). The use of conservative measures prior to sling incision was identified in 43.8 % of subjects, with office-based excision having been performed in 31.6 % (18/56), a trial of vaginal estrogen in 36.8 % (21/56), and a trial of anticholinergic medications for overactive bladder in 36.8 % (21/56) of subjects. Of the subjects, 60 (45.4 %) underwent mesh excision for voiding dysfunction, 21 (16.2 %) underwent excision for both pain/exposure and voiding dysfunction, and the remaining 49 (37.7 %) underwent surgical excision for both pain/exposure and voiding dysfunction. The histological data is shown in

Table 2 Demographics of patients who underwent midurethral sling excision

N=130	Voiding dysfunction (*N*=60)	Pain/mesh exposure (*N*=21)	Voiding dysfunction and pain/mesh exposure (*N*=49)	*p* value
Mean age (SD)	54.8 (10.8)	50.2 (8.1)	52.2 (11.8)	0.2
Mean BMI (SD)	30.0 (7.8)	30.8 (5.6)	29.1 (6.3)	0.6
Median parity (range)	2 (0–6)	2 (0–7)	2 (0–6)	0.6
Diabetes mellitus (%)	7.14	9.5	2.0	0.4
Tobacco history (%)				0.8
Current	30.0	19.0	30.6	
Past	21.7	42.9	18.4	
Never	48.3	52.4	51.0	
Chronic steroid use (%)	1.7	0	0	0.6

Table 3. The most common finding in all groups was mild inflammation (found in 53.9 % of specimens) and only 9.2 % of specimens showed no inflammation. Moderate or marked inflammation was noted in 48 (36.9 %) specimens. Specimens in the voiding dysfunction only group were found to have higher amounts of moderate inflammation compared to the pain and/or exposure group and the voiding dysfunction and pain/exposure group and this finding was statistically significant: 47.6 vs 26.7 vs 36.7 %, $p=0.02$. Furthermore, pairwise testing showed that the median grade of inflammation was higher in the voiding dysfunction group compared to the other 2 groups: 2 (range 1–3) in the voiding dysfunction group, 1 (range 0–3) in the pain and/or exposure group, and 1 (0–3) voiding dysfunction plus pain and/or exposure group.

Moderate fibrosis was seen in 61 % of pathological specimens with no difference found between the three groups. Almost all subjects (89.2 %) demonstrated giant cell reaction with no differences between groups. Figure 1a shows excised midurethral mesh and vaginal tissue with the representative histological grading system.

Discussion

The optimal implant into human tissue has been described as one that does not elicit a significant host-tissue reaction, is lightweight, maintains flexibility, and provides long-term support [10]. In 1997, Amid created a classification of biomaterials used in abdominal wall hernia repair according to the specific properties of each mesh including filament type, pore size, and weight. Of the four types of mesh in this classification system, polypropylene mesh, which is used in most midurethral slings, is classified as a type 1 mesh and contains many of the desirable properties listed above. The host response to polypropylene mesh has been described in human and animal models [15]; however, the response in the human vagina has not been well studied.

In our study, we found that the majority of vaginal mesh was removed for voiding dysfunction alone, with a large proportion also undergoing excision for both voiding dysfunction and pain and/or mesh exposure. The most common histopathological responses in all groups, including those with voiding dysfunction alone, were mild inflammation, moderate

Table 3 Histological comparison between groups

	Voiding dysfunction (*N*=60)	Pain/mesh exposure (*N*=21)	Voiding dysfunction and pain/mesh exposure (*N*=49)	*p* value
Inflammation (%)				0.02
None (0)	0	15	6.1	
Mild (1)	42.9	56.7	55.1	
Moderate (2)	47.6	26.7	36.7	
Marked (3)	9.5	1.7	2.0	
Fibrosis (%)				0.6
None (0)	0	0	2.0	
Mild (1)	23.8	25.0	22.5	
Moderate (2)	71.4	70.0	59.2	
Marked (3)	4.8	5.0	16.3	
Giant cell reaction (%)	90.5	86.7	89.2	0.7

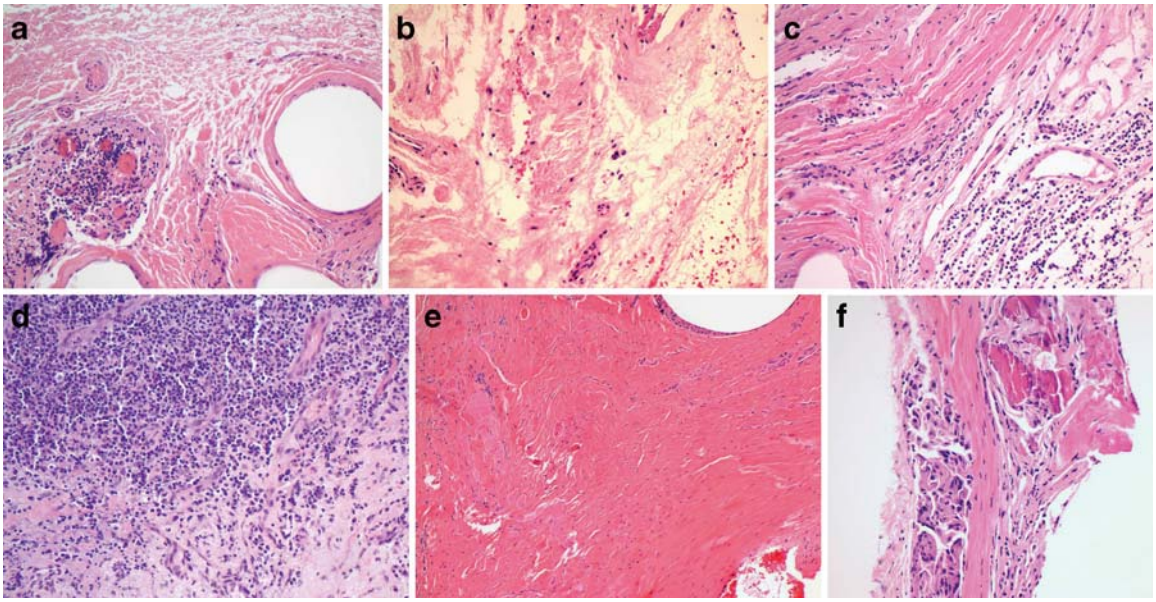

Fig. 1 Representative histological findings identified following mesh excision. **a** Grade 0 inflammation and grade 1 fibrosis: delicate loose fibrovascular connective tissue with scattered fibroblasts. Chronic inflammatory cells are absent. **b** Grade 1 inflammation: a sparse infiltrate of chronic inflammatory cells associated with mesh material and foreign body giant cell reaction. **c** Grade 2 inflammation and grade 2 fibrosis: chronic inflammatory cells are more numerous and are associated with foreign body giant cell reaction with extension into the adjacent connective tissue. The connective tissue is focally dense and fibrous. **d** Grade 3 inflammation: a markedly cellular chronic inflammatory infiltrate with lymphocytes and numerous plasma cells is associated with the foreign body giant cell reaction and extends into adjacent connective tissue. **e** Grade 3 fibrosis: dense fibrous connective tissue forming a fibrotic nodule. **f** Presence of giant cell reaction: numerous multinucleated giant cells with interspersed chronic inflammatory cells surround synthetic mesh material

fibrosis, and giant cell reaction. These results are consistent with some of the findings of Smith et al. [16]. In their study, 47 specimens of explanted vaginal mesh were reviewed histologically. Fibrosis was identified in 70.1 % of specimens. However, only 18.8 % of their specimens were noted to have a foreign body giant cell reaction and inflammation was reported in 10.4 % of the pathological specimens [16]. These results differed from ours, and this may be because the authors looked at all cases of explanted vaginal mesh for pelvic organ prolapse, while our study was designed to examine excised midurethral mesh only. Also, the grading system and criteria for inflammation that the authors used are not defined and may have differed from ours. Conversely, Wang et al. also looked at 20 pathological specimens of mesh explanted for failed anti-incontinence procedures and found them to mostly have moderate inflammation and foreign body reaction, which is consistent with our findings [19].

Subjects with voiding dysfunction but not pain or mesh exposure were found to have more inflammation than subjects who underwent mesh excision for pain and/or mesh erosion and those with both voiding dysfunction and pain/mesh exposure. This difference may be related to timing of mesh excision in patients with only voiding dysfunction. Voiding dysfunction is usually diagnosed in the immediate postoperative period, and if attributed to midurethral sling placement, mesh excision often occurs sooner in these patients than in those who present with pain and/or exposure. As a result, mesh specimens from these subjects would be expected to have higher degrees of inflammation compared to others as the healing process from the placement of the original implant would still be present. In our study population, only 72/130 (55 %) index surgery operative reports were available for review, and therefore we were unable to accurately report and compare time from index surgery to excision among the three groups in order to confirm this hypothesis.

Additionally, our findings could be a result of tissue remodeling/fibrosis that may occur following placement of a midurethral sling [17–19]. One could hypothesize that in the presence of an inflammatory state, the sling may retract and/or shrink therefore applying undue tension along its path, which in turn may lead to increased levels of voiding dysfunction.

Approximately 90 % of the pathological specimens in our study were found to have evidence of a giant cell reaction. This is consistent with what occurs after implantation of a biomedical device and is referred to as the "foreign body reaction" [15]. This is an immunologically mediated process that takes place at the cellular level and initially occurs during the first few weeks following implantation, but remains present at the device/host-tissue level for a lifetime depending on what kind of biomaterial is used [20]. Most of what we know about this process is a result of research that has looked at the host-tissue response with various biomaterials and/or mesh following implantation in both human and animal studies.

The strengths of our study include a large cohort of subjects. Additionally, all pathological specimens were rereviewed by a single pathologist who was blinded to the indication for mesh excision. Finally, our constructed histological grading system allowed for a systematic evaluation of individual specimens and allowed us to compare outcomes between the three groups. However, we do acknowledge that our grading system was specifically developed for this investigation and has not yet been validated by other facilities. The major limitation to this study is its retrospective design. We did not have access to all of the index surgery operative reports, and therefore we relied on subject recall as documented in the electronic medical record for some of our data. This limited our ability to analyze potential risk factors that may have led to increased levels of inflammation. These include the date of the index mesh placement, type of mesh utilized, and the surgical approach (i.e., transobturator or retropubic) that was performed. Additionally, not all subjects who underwent revision of their sling had pathological specimens for review. It is unknown if the findings at the time of the surgical procedure, i.e., signs of inflammation/infection or litigious indications, may have led to increased pathological submission. Lastly, the medical record was used to classify patients into their respective groups, which is also subject to information bias. Attempts were made to minimize these biases and measures were taken to ensure that strict criteria were used to classify subjects, and one researcher was responsible for all data collection.

Vaginally placed midurethral sling mesh that is excised for voiding dysfunction demonstrates elevated levels of inflammation compared to mesh that is excised for pain and/or exposure. Giant cell reaction also appears to be a ubiquitous finding in excised vaginal mesh, and the vaginal tissue response to midurethral mesh is histologically similar for fibrosis and giant cell reaction in all patients. We therefore can conclude that some histopathological indices may differ among specimens, and these differences may be related to the indication for midurethral mesh excision. While the clinical implications of this finding remain unclear, our results contribute to the limited data that exists on this subject, and future studies should aim at further investigating the host-tissue response as it relates to transvaginal mesh placement.

Conflicts of interest None.

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